DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 77N–0094]

RIN 0905–AA06

Labeling for Over-the-Counter Oral Drug Products Containing Aspirin, Buffered Aspirin, or Aspirin in Combination With an Antacid

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations to require that the labeling for over-the-counter (OTC) oral drug products that contain aspirin, buffered aspirin, and aspirin in combination with an antacid prominently bear a statement advising persons using these products to consult a doctor before taking them for their heart or for other new uses of aspirin. This labeling does not apply to aspirin in combination with acetaminophen, a diuretic, or any cough-cold ingredients. FDA is taking this action to inform the public about the risks associated with long-term, unsupervised use of these products and of the importance of medical evaluation and supervision for safe long-term use of these products.

DATES: Written comments by December 20, 1993. Written comments on the agency's economic impact determination by December 20, 1993. FDA is proposing that the final rule based on this proposal be effective 6 months after the date of publication of the final rule in the **Federal Register**.

ADDRESSES: Written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

SUPPLEMENTARY INFORMATION:

I. Introduction

In the **Federal Register** of November 16, 1988 (53 FR 46204), FDA published, under § 330.10(a)(7) (21 CFR 330.10(a)(7)), a notice of proposed rulemaking, in the form of a tentative final monograph, that would establish conditions in part 343 (21 CFR part 343) under which OTC internal analgesic, antipyretic, and antirheumatic drug products are generally recognized as safe and effective and not misbranded. In the professional labeling in § 343.80, the agency proposed a number of indications for products containing aspirin, buffered aspirin, or aspirin in combination with an antacid. The agency acknowledged that information about these uses of aspirin products (e.g., reducing the risk of myocardial infarction in patients with a previous infarction or unstable angina pectoris) has appeared in newspapers and magazines and on television and radio. In addition, the agency recognized that some manufacturers have included statements in the labeling of their OTC aspirin drug products that advise people to see their doctor for other (or new) uses of aspirin. The agency stated that because such information may be of benefit, it had no objection to a general statement of this type being included in the product's labeling. The agency expressed concern, however, that people may read or hear this information and self-medicate with an OTC aspirin drug product for one of these conditions without consulting their doctor.

Accordingly, the agency emphasizes that people should use aspirin for professional indications only under a doctor's supervision. Aspirin, particularly if used for a long period of time, may cause serious side effects, including bleeding and stroke (Ref. 1). In addition, people should not self-medicate for professional indications because they lack the necessary training to determine whether they are likely to benefit from this treatment. Because of these concerns, the agency stated that any information provided in aspirin product labeling about other (professional) uses must be accompanied by a counterbalancing statement that the product should not be used for more than 10 days without consulting a doctor. This period of use is consistent with the OTC labeling proposed for aspirin in the tentative final monograph. In § 343.50(f) of the tentative final monograph the agency proposed the following optional statement for aspirin products: "See your doctor for other uses of" [insert name of ingredient or trade name of product]", but do not use for more than 10 days without consulting your doctor because serious side effects may occur." The agency invited specific comment on this statement or other alternative labeling, the appropriate placement for the statement in labeling, whether the 10-day limitation on use should be an integral part of any such statement, and whether this information should be part of the required labeling for aspirin products (53 FR 46204 at 46252).

II. Summary of the Comments Received

Two comments requested that the optional statement proposed in § 343.50(f) be shortened to include only the part that reads: "See your doctor for other uses of" [insert name of ingredient or trade name of product]. The comments requested the agency not to require the part of the statement that reads: "but do not use for more than 10 days without consulting your doctor because serious side effects may occur."

One comment stated that the full statement was confusing and "counter productive" because it "sends mixed messages" and achieves the opposite effect of what FDA intended. The comment contended that the statement alerts people to confer with their doctor about nonlabeled uses, while cautioning them against long-term use without consulting a physician. The comment added that the language is likely to unnecessarily frighten individuals for whom long-term aspirin therapy has been prescribed. The comment stated that highlighting the risk of serious side effects is inappropriate for patients prescribed aspirin by their physician, when a risk-benefit judgment has been made. The comment added that the warning could discourage patients from taking aspirin that had been prescribed by their doctor. According to the comment, the result could be dangerous if the aspirin is being used to treat a serious condition. The comment also argued that information against long-term use without a physician's direction and a list of adverse effects already appear in the warnings and directions. The comment added that inclusion of side effects in the proposed statement is redundant. Finally, the comment stated that there is controversy over whether long-term aspirin use leads to increased incidence of side effects. The comment referred to the absence of a significant difference in gastrointestinal side effects between the placebo and aspirin study groups in the Physicians' Health Study (Ref. 2).

The second comment contended that the part of the statement about side effects and not using the product for more than 10 days causes several problems. It suggests that people can experiment with nonlabeled uses for less than 10 days without consulting a doctor. It is redundant because it repeats the restriction on use for more than 10 days already set forth in the standard warnings. It is ambiguous with respect to its reference to serious side effects because it refers to nonlabeled uses. The

comment stated that any nonlabeled use without consulting a physician should be discouraged, but argued that the proposed language would not achieve that purpose.

III. The Agency's Conclusions on the Comments

The agency disagrees with the comment asserting that the optional labeling statement was contrary to the agency's objective for this labeling. The objective of the statement is to inform individuals, who may be informed (by the media or advertisements) about other new uses of aspirin products, that such uses are not risk-free, that adverse effects are associated with these uses, and that the safe and effective use of the drug product for new uses requires the advice and supervision of a physician. The agency is concerned that people may not understand the risks associated with new uses of familiar products, long available without prescription, especially uses that involve lower doses for a long period of time.

The agency disagrees with one comment's contention that reference to serious side effects is redundant and would unnecessarily frighten patients taking the drug on the advice of their doctor. The general reference to serious side effects in the statement does not repeat other cautionary information found in the OTC product labeling. The reason for advising people of potential, serious side effects with new uses is to encourage them to discuss such uses with their doctor and to inquire about potential risks. The agency does not believe that the proposed statement would frighten into noncompliance those people for whom chronic aspirin therapy has already been prescribed by their doctor. On the contrary, the statement should reassure patients that they have taken appropriate precautions by checking with their doctor prior to taking the product. Patients under a doctor's care, for whom reference to serious side effects raises additional questions, are likely to discuss their concerns with their doctor if they have not already done so. People considering self-medication for a new use are more likely, after having been alerted to the potential for side effects, to discuss risks with their doctor.

With respect to the comment that controversy exists over increased risk of side effects with long-term use, the agency notes that the comment confined its consideration of risk to gastrointestinal side effects alone, as reported in the Physician's Health Study (ref. 2). The incidence of gastrointestinal bleeding in this large trial was not different between the aspirin group and the placebo group. However, the Steering Committee of the Physicians' Health Study Research Group, in its preliminary report, specifically noted that this finding was partly attributable to the prerandomization run-in phase, which excluded those unable to tolerate aspirin, and partly related to the particular dose and regimen employed in the study. In addition to gastrointestinal bleeding, however, the study recorded a nonsignificant increase of total strokes in this selected population and a significantly increased number of moderate-to-severe or fatal hemorrhagic strokes. Similar observations have been reported in other studies. A study in healthy British doctors reported a nonsignificant increase in fatal or disabling strokes in the aspirin group (Ref. 3). In the "Swedish Aspirin Low-dose Trial" (SALT) (Ref. 4), while there were only slightly more frequent gastrointestinal events (excluding bleeding) in patients taking 75 milligrams of aspirin, a significant excess of total bleeding episodes occurred in the 676 subjects in the aspirin group compared with the 684 subjects taking placebo (7.2 versus 3.2 percent; p=0.001). Significantly more bleeding events in patients on aspirin were considered severe or resulted in discontinuation of the study drug (p=0.04); five patients on aspirin suffered fatal hemorrhagic strokes compared to none on placebo (p=0.03). In conclusion, a narrow focus on the incidence of only gastrointestinal bleeding in the Physician's Health Study (Ref. 2) cannot be extrapolated to exclude all risks that may be associated with professional uses of aspirin in an unselected population.

The agency agrees, however, that including the restriction against use for more than 10 days without consulting a doctor in the optional warning repeats the language set forth in the standard warning and is, therefore, redundant. The agency also agrees that such a statement, made in regard to new uses, may be incorrectly interpreted to imply that people can safely take the product for such uses for less than 10 days without consulting a doctor. Therefore, the agency is deleting that portion of the statement.

IV. The Agency's Proposal

Since publication of the tentative final monograph on November 16, 1988, information on the use of aspirin for preventing heart attack and stroke has continued to appear in the news media. Thus, public awareness of new uses of aspirin has continued to increase without commensurate awareness of risks associated with such uses. Given this publicity, the long-established availability and widespread use of OTC aspirin products, and the public perception of the safety of aspirin based on its long history for short-term uses, the agency believes that increasing numbers of individuals might initiate chronic self-medication for new uses without the advice of a doctor. The agency is aware that some manufacturers have voluntarily included the optional statement proposed in § 343.50(f) of the tentative final monograph, or a similar statement, in the labeling of their OTC aspirin products. However, there are many aspirin products in the marketplace without a labeling statement of this type. The agency considers it very important to have a required labeling statement on all OTC oral aspirin drug products to inform people of the need to see a doctor prior to using the product for any professional indications. The agency considers this need important enough to take this labeling statement out of the proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products before completion of the entire monograph. The agency proposes that the statement appear in § 201.314 (21 CFR 201.314) until the final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products is completed. Then, it will be incorporated into the final monograph.

While professional labeling proposed in the tentative final monograph also includes indications for rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis (degenerative joint disease), ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, and fibrositis, the agency is concerned primarily with the use of aspirin products to reduce the risk of cardiovascular and cerebrovascular events. Such use is more likely to be initiated by otherwise healthy people who are not under a doctor's care. Therefore, the agency is proposing that this new labeling statement be required for use on products containing aspirin ingredients identified in proposed § 343.10(b)(1) and (b)(2), and § 343.20(b)(3). The labeling of these products would be required to state, in a prominent place, the following: "IMPORTANT: See your doctor before taking this product for your heart or for other new uses of aspirin, because serious side effects could occur with self treatment." This labeling statement does not apply to aspirin used in

combination products described in § 343.20(a), (b)(2), and (b)(4).

Because the statement has been changed since it was originally proposed in the tentative final monograph, the agency is proposing the new statement for public comment in this document. The agency invites specific comment whether the introductory word "WARNING" would be preferable to the word "IMPORTANT" and whether other words (e.g., "unlabeled") would be preferable to the word "new" in this labeling statement.

The agency believes that this important information should be conveyed in product labeling at the earliest possible date. Accordingly, the agency is proposing that this new labeling statement become effective 6 months after the date of publication of the final rule in the **Federal Register**. Further, the agency encourages manufacturers of OTC oral drug products containing aspirin, buffered aspirin, and aspirin in combination with an antacid to implement this labeling voluntarily as of the date of publication of this proposal, subject to the possibility that FDA may change the wording of the labeling statement as a result of comments filed in response to this proposal. Because FDA is encouraging the proposed new labeling statement to be used on a voluntary basis at this time, the agency advises that manufacturers will be given ample time after publication of a final rule to use up any labeling implemented in conformance with this proposal.

References

(1) Feldmann, E. G., editor, "Handbook of Nonprescription Drugs," 9th ed., American Pharmaceutical Association, Washington, p. 68, 1990.

(2) The Steering Committee of the Physicians; Health Study Research Group, "Preliminary Report: Findings from the Aspirin Component of the Ongoing Physicians' Health Study," *New England Journal of Medicine*, 318:262–264, 1988.

(3) Peto, R., et al., "Randomized Trial of Prophylactic Daily Aspirin in British Male Doctors," *British Medical Journal*, 296:313–316, 1988.

(4) The SALT Collaborative Group, "Swedish Aspirin Low-dose Trial (SALT) of 75 mg Aspirin as Secondary Prophylaxis after Cerebrovascular Ischaemic Events," *Lancet*, 338:1345–1349, 1991.

V. Economic Impact

FDA has examined the regulatory impact and regulatory flexibility implications of this proposed rule in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354). This proposed regulation imposes direct one time costs associated with changing product labels to include the required labeling statement. FDA estimates those costs to total less than $5 million. Therefore, the agency has determined that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities, as defined by the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC oral drug products containing aspirin, buffered aspirin, and aspirin in combination with an antacid. Types of impact may include, but are not limited to, costs associated with relabeling or repackaging.

Comments regarding the impact of this rulemaking on OTC drug products containing aspirin, buffered aspirin, and aspirin in combination with an antacid should be accompanied by appropriate documentation. A period of 60 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

VI. Environmental Impact

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before December 20, 1993, submit to the Dockets Management Branch (address above) written comments on the proposed regulation. Written comments on the agency's economic impact determination may be submitted on or before December 20, 1993. Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR Part 201 be amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 530–542, 701, 704, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg-360ss, 371, 374, 376); secs. 215, 301, 351, 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 264).

2. Section 201.314 is amended by adding new paragraph (i) to read as follows:

§ 201.314 Labeling of drug preparations containing salicylates.

* * * * *

(i)(1) The labeling of orally administered over-the-counter drug products containing aspirin, buffered aspirin, and aspirin in combination with an antacid subject to this paragraph is required to prominently bear the following statement: "IMPORTANT: See your doctor before taking this product for your heart or for other new uses of aspirin, because serious side effects could occur with self treatment." This labeling statement does not apply to aspirin used in combination with acetaminophen, any cough-cold ingredient, and any diuretic ingredient.

(2) Any product subject to this paragraph that is not labeled as required by this paragraph and that is initially introduced or initially delivered for introduction into interstate commerce after [insert date 6 months after date of publication of the final rule in the **Federal Register**], is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

Dated: June 11, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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